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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,507	01/23/2004	Bruce R. Line	100413-5001	5234

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,507	LINE ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-86* is/are pending in the application.

4a) Of the above claim(s) *27,28,41-71 and 82-84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,29-40,72-81,85 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/23/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1 – 40, in the reply filed on 9/4/2007 is acknowledged. The traversal is on the grounds that Groups I and IV are directed toward microparticles comprising a core, at least one radioactive therapeutic agent attached to said core, and are classified in the same class and subclass by the Examiner for searching purposes. Applicant argues that the Examiner has not demonstrated why searching both groups would be burdensome.

It is noted by the Examiner that an examination and search burden for patentably distinct inventions or species due to their mutually exclusive characteristics does not necessarily require separate classification to show that burden exists. For example, burden may be shown by demonstrating that the search for distinct inventions may require a different field of search (e.g. employing different search queries) and/or that the prior art applicable to one species would not likely be applicable to another species; and/or that the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

In the instant case, Groups I and IV were restricted due to the materially different design of the microparticles in the respective groups. However, the restriction requirement between Groups I and IV is no longer applicable in view of the amendment to claim 72 in the instant application. Since Group IV now requires the presence of a linking carrier, the microparticles no longer have a materially different design and the

restriction requirement is hereby WITHDRAWN with respect to Groups I and IV. Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement with regard to any additional groups. Accordingly, the election with regard to groups II, III and V has been treated as an election without traverse and is hereby made FINAL (MPEP § 818.03(a)). Applicant's election of dendrimer as the linking carrier in the reply filed 12/19/2007 is also acknowledged.

Status of Claims

Claims 1 – 86 are pending, of which claims 41 – 71 and 82 – 84 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 27 and 28 are withdrawn from consideration at this time as being drawn to non-elected species. Claims 1 – 26, 29 – 40, 72 – 81, 85 and 86 are readable upon the elected invention and species and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 6, 12, 13, 16, 18, 29, 30, 35 – 40, 85 and 86 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothman *et al.* (US 4,115,536).

Rothman discloses agents for intravascular administration for diagnostic and/or physiological investigations which contain minute radioactive particles in a physiologically acceptable liquid (abstract). The particles preferably have a particle size of 0.1 – 300 micrometers and are labeled with at least one metallic radionuclide, said particles being insoluble but swellable in water, and comprising polymer groups containing hydroxyl groups, preferably polymerized carbohydrates or sugar-alcohols. The particles have covalently bound chelate-forming groups to which the radionuclide is bound in chelate-forming groups (column 2, lines 1 – 25). The particles may be non-degradable or biodegradable (column 4, lines 66+; column 7, line7). Particle size may be in the range of 5-60 micron, or 5-15 micron, depending on the application of the particles (column 7, lines 55+). The radionuclide may be ^{169}Ytterbium (e.g. gamma emitting), see Examples. The particles are designed to overcome the problem of leaching of radionuclides (see column 1, lines 13 – 66).

Claims 1 – 9, 12, 16, 17, 30 – 36, 38, 39, 40, 72– 81, 85 and 86 are rejected under 35 U.S.C. 102(e) as being anticipated by Burns *et al.* (US 7,276,254).

Burns discloses polymeric microspheres for biomedical applications having a biomedical functional material attached thereto, and an average particle diameter from about 1 to about 15 microns. The biofunctional material may be a radioactive material (abstract). The particles may also range in size from about 0.5 to about 20 microns

(column 5, line 5). Any suitable polymer may be used to form the microspheres, for example polyesters, polyacrylate, polymethacrylate, etc. (column 5, lines 15 – 65). The particles may be subjected to optional surface treatment in order to attach or alter functional groups present on the surface of the microspheres (column 15, lines 40 – 50). Functional groups can be reacted with materials that may in turn act as linkages to biological materials, ligands (column 16, lines 38 – 50). Biological or medical materials can be attached to the surface of the microspheres by covalent bonding, complexation, adsorption and the like (column 19, lines 4 – 6). In a preferred embodiment, the radioactive constituent is chosen that so when administered, the radioactive microspheres emit a therapeutic intensity and amount of short-range beta or gamma radiation, but will not emit a significant amount of unwanted beta or gamma radiation (column 19, lines 18 – 26). Yttrium and/or phosphorous may be incorporated into the microspheres (column 19, lines 33 – 63). Regarding claims 31 and 32, it is noted that the functional recitation that the particle has the claimed density range is not given patentable weight to distinguish over Burns. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Since Burns discloses microspheres comprising the same polymers as those claimed, they would inherently be capable of having the same density.

Claims 1 – 7, 12 – 14, 16 - 18, 30 - 32, 35, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Domb *et al.* (US 5,578,325).

Domb discloses injectable particles that are not rapidly cleared from the bloodstream by macrophages of the reticuloendothelial system (abstract). Nonlinear block copolymers containing one or more hydrophilic polymers and one or more hydrophobic bioerodible polymers are prepared. The hydrophilic polymer may be PEG, the hydrophobic polymer may be polylactic acid, polyphosphazenes, etc. Ligands can be attached to one or more polymer chains to achieve a variety of properties for a variety of applications (column 2, lines 46+). Materials incorporated onto or within the polymers include biologically active materials such as antibodies, etc. (column 3, lines 14 – 23). Microparticles can be prepared by forming the block copolymers in sizes ranging from 1 – 1000 micron (column 9, line 53 – column 10, line 43). See column 12 and also Example 21. Indium-111 can be directly attached to the multiblock copolymer by complex formation via DTPA. Regarding claims 31 and 32, it is noted that the functional recitation that the particle has the claimed density range is not given patentable weight to distinguish over Burns. "Products of identical chemical composition cannot have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure or composition as that which is claimed, the properties applicant discloses and/or claims are necessarily present. See *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Since Domb discloses microspheres comprising

the same polymers as those claimed, they would inherently be capable of having the same density.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 26, 29 – 36, 38 – 40, 72 – 81, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns *et al.* (US 7,276,254), in view of Wu *et al.*(Bioorg. Med. Chem. Lett., 1994, 4, p. 449-454), in further view of Danthi *et al.* (US 2003/0133972) and Lugade *et al.* (US 7,241,883).

Burns discloses polymeric microspheres for biomedical applications, as set forth above. The particles may be subjected to optional surface treatment in order to attach or alter functional groups present on the surface of the microspheres (column 15, lines

40 – 50). Functional groups can be reacted with materials that may in turn act as linkages to biological materials, ligands (column 16, lines 38 – 50). Biological or medical materials can be attached to the surface of the microspheres by covalent bonding, complexation, adsorption and the like (column 19, lines 4 – 6). In a preferred embodiment, the radioactive constituent is chosen that so when administered, the radioactive microspheres emit a therapeutic intensity and amount of short-range beta or gamma radiation, but will not emit a significant amount of unwanted beta or gamma radiation (column 19, lines 18 – 26). Yttrium and/or phosphorous may be incorporated into the microspheres (column 19, lines 33 – 63).

Burns fails to specifically recite the identity of the moiety which may be employed to provide linkage, covalent bonding, complexation of the biological material, e.g. radioactive constituent, onto the microsphere. It is for this reason that Wu is joined,

Wu discloses polyamidoamine dendrimers modified to chemically react with DOTA and DTPA type bifunctional metal chelators and coupled to monoclonal antibody. DTPA and DOTA-dendrimer-antibody constructs were easily labeled with ^{90}Y, ^{111}In, ^{212}Bi, suggesting use of the constructs for use in mAB guided radiotherapy or imaging (abstract).

Wu teaches dendrimer-DOTA-^{90}Y conjugated to antibody, rather than microsphere. However, the use of dendrimer as a linking agent for conjugation to microsphere is known in the art, as shown by Danthi and Lugade.

Danthi discloses that dendrimers can be readily used as linking carriers by employing a variety of chemical conjugation techniques to attach the targeting entity

and therapeutic entity. For example, a dendrimer having a disulfide (--S--S--) bond in its core. The final external layer of the dendrimer can be capped with a reactive group such as an amine or carboxyl group. These reactive groups can then be derivatized with either targeting entities or therapeutic entities (or, in some cases, a mixture of both). The core disulfide bond can then be reduced to a thiol, and the complementary entity attached via the thiol functionality. That is, if a therapeutic entity had been attached to the external layer of the dendrimeric linking carrier, upon reduction and formation of the thiol functionality, a targeting entity can be attached via the free --SH group (paragraph 0120 – 0122).

Lugade also discloses that dendrimers are useful linkers by which to attach functional groups to microsphers (see column 10, lines 5 – 31).

It would have been obvious to one having ordinary skill in the art at the time of the instant invention to provide the radioactive yttrium constiutent of Burns in the form of a dendrimer-linked DOTA or DTPA carrier when the teachings of Burns are taken in view of Danthi, Lugade and Wu. Burns does not specifically teach the identity of the moiety which is used to introduce the radioactive constituent (e.g. yttrium), thus one of ordinary skill in the art would have been motivated to seek out a suitable moiety which would be capable of linking, covalent bonding, complexation onto the microsphere for radiotherapy. Dendrimer-conjugated DOTA or DTPA are known in the art to be a suitable carrier for radioactive yttrium, as shown by Wu. Wu discloses dendrimer-DOTA-^{90}Y (and other radionuclides) for the purposes of radiotherapy and imaging, but does not teach their conjugation to microsphere. However, dendrimer is known to be a

suitable linking moiety to conjugate a functional group to microsphere as shown by Danthi and Lugade. It would have been obvious to one of ordinary skill to utilize such a dendrimer-DOTA conjugate to introduce radioactive yttrium to the microspheres of Burns by application to the formed microspheres, and one would have had a reasonable expectation of success in doing so, because Burns teaches radioactive yttrium to be useful when incorporated onto microspheres for emitting radiation that will spare healthy tissue remote from the tumor site in which the microsphere is embedded (column 19, lines 8 - 64) and because Wu teaches dendrimer-DOTA as a successful carrier for ^{90}Y for radiotherapy/imaging.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS